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## Asthma Bronchiale, etterige (bacteriele) bronchitis en het endocrine systeem

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

1952

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Israels, A. A. (1952). Asthma Bronchiale, etterige (bacteriele) bronchitis en het endocrine systeem. Groningen: s.n.

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## SUMMARY

Some aspects are studied of the relations between bronchial asthma, bacterial (purulent) bronchitis and the endocrine system, particularly the pituitary-adrenal system.

In chapter I the results are given of a study of bacterial bronchial infection in a series of 300 asthmatic patients. In the first paragraphs we gave the subdivision of this group in age and sex (table 1, fig. 1, pp. 8 a. 9), duration of asthma (table 2, fig. 2, pp. 9-10), year of appearance of asthma (table 3, fig. 3., pp. 10-11), age of onset of asthma and of other allergic manifestations (pp. 11-13). Dermatological conditions (p.13) and oto-rhino-laryngological complications (p.14) in this group are shortly summarized. In this group of 300 patients 167 stated that asthma occurred in their family (table 9, p. 15).

In the third paragraph the results of examination of the sputum of these 300 patients are compiled. The macroscopic aspect of every specimen was noted, and Gram-stained preparations of washed flakes were used for bacteriological examination. Further identification of the microorganisms, found in the Gram-stained slides, are done with simple standard cultural methods, but are not recorded in this study. A wet washed flake of every sputum specimen was stained in an eosin-formalin-solution and the percentage of eosinophilic cells was noted. The washing procedure, as introduced by Mulder <sup>1)</sup>, proved to be of the greatest importance in the study of unspecific bronchial and pulmonary infections.

In this way generally no polygonal epithelial cells from the nasopharynx and no bacteria from that region are found in the Gram-stained slides or in culture media. The results accord very well with bacterial findings in surgically extirpated parts of lungs, in Monaldi suction fluid or in lung punctates, and the results are fully reproducible.

One third of our 300 patients showed mucous bronchial sputum without bacteria and with a high percentage (70-100%) of eosinophilic cells, about one third showed purulent sputum with only few eosinophilic cells and with bacteria (one half of them *haemophilus influenzae* Pfeiffer, the other half of them other bacteria), one third showed mucous or muco-purulent sputum without bacteria and with only few or no eosinophilic cells (table 10, p.18). However, this situation is not at all stable: one sees infection appear and disappear, with changes of the macroscopic and microscopic appearance. A typical example is given in p.20.

In table 12 and fig.6 (p.20-21) the results are given of a division of different age groups in patients with purulent sputum with *haemophilus influenzae*, patients with other bacteria, and asthma patients with mucous sputum with many eosinophilic cells but without bacteria. It is shown that in higher age groups infection is *not* more frequent than in younger patients, as sometimes is suggested. In table 13 and fig.7 (p.21-22) the incidence of patients with the same three qualities of sputum is noted in groups

1) Mulder, J.: Acta Med. Scand. 94, 98, 1938.



with different duration of asthma. In patients with long duration of asthma we showed that there is no higher incidence of bronchial infection. The combination of asthma and bronchial infection appears to be not stable, for which several causes are suggested: 1) sometimes a bronchial infection is a fatal complication. 2) sometimes asthma disappears when the infection is stable. 3) more frequent infections in asthma disappear spontaneously. The first and second possibility will be explained later on. It seems to us, that many patients, suffering from bronchiectasis, are hidden asthmatics. A constant infection, working as a „stressor agent” on the pituitary-adrenal system, may have a beneficial action of the asthmatic dyspnoe, comparable with the action of ACTH.

In table 14, p.23 the same three groups with different sputum qualities (haemophilus influenzae, other bacteria, and eosinophilia) are compared with the age of onset of allergic phenomena. It is shown that no greater incidence of bronchial infections was found in asthmatic cases which began at older age.

On page 24-28 the importance of the role of a bronchial infection in the pathogenesis of a cor pulmonale in asthma is stressed. This study from our clinic will be published elsewhere <sup>1)</sup>.

On the next pages it is shown, that in the asthmatic patients with a bacterial bronchial infection, asthma occurred in the family for 49% (53% in the total group of 300 patients had asthma in their family). 71% of the infected cases gave a case history of allergens (70% of the total group showed allergens in the anamnesis). It is concluded from these findings, that a subdivision of asthmatic cases into an infected and a non infected group does neither parallel a partition into a non allergic („intrinsic”) and an allergic („extrinsic”) group, nor a partition into groups without and with hereditary („atopic”) factors.

No study has been made of cutaneous reactions on bacterial products. It seems to us, that cutaneous reactions to pneumococci and streptococci in asthma, as are frequently reported in the literature, must be of unspecific origin. These microorganisms do exist in the pharynx of the majority of normal (and asthmatic) individuals, but in only few cases they are responsible for the purulent bronchitis in asthma.

Fig.9 p.29 shows the number of circulating eosinophilic cells to be significantly higher in the non infected cases than in the cases with a bronchial infection. This fact might seem to express a more „intrinsic” and less „allergic” origin of asthma in infected cases. If infection is considered as a „stressor agent” for the pituitary-adrenal system, the depression of the eosinophilia in infected cases may be seen as a result of that action. Later on (p.102-104) it will be shown that during a bronchial infection the excretion of neutral 17-ketosteroids is also higher.

On p.30-38 the results are given of a study of bronchograms, which were made in 58 of these 300 asthmatic patients. Plate 1-12 give representative illustrations of the different findings. The incidence of the various pictures and their correlation with bron-

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2) Orie, N.G.M., Buchem, F.S.P.van, Homan, B.: Chronic cor pulmonale. Acta Med. Scand., to be published.



chial infection was studied. The theory of Watson en Kibler, that the majority of bilateral basal bronchiectasis has an allergic origin, seems to us to be correct. The beneficial effect of a bronchial infection as a „stressor agent” in bronchiectasis may be in part responsible for the fact, that in these patients asthmatic complaints relatively seldom are heard.

The second chapter has been devoted to a study of the effect of ACTH in asthma. The evaluation of any therapeutic measure in bronchial asthma is difficult for several reasons: 1) spontaneous remissions are frequent. 2) „spontaneous” remissions after admission in a clinic are very frequently seen. 3) asthma patients are more or less suggestible, as are sufferers from other diseases. 4) the objective criteria as vital capacity, expiration velocity and residual volume are very inconstant in these persons, depending on the presence of attacks. Consequently specific treatment in our series was started only after an observation period in the clinic of at least 10 days. In this way several patients admitted in an asthmatic state, improved „spontaneously” without ACTH. After at least ten days placebo injections or infusions were given to 15 patients, in 5 cases this was not given for several reasons. In 4 cases some objective or subjective improvement was noted during placebo therapy, in 11 cases no improvement was seen. In 20 cases, treated with ACTH, subjective improvement was seen 13 times, dubious 4 times, no improvement 3 times. Objective improvement 11 times, dubious 3 times, no improvement 6 times. These 20 patients, treated with ACTH, were the most resistant ones out of several hundreds of asthmatics, all other therapy was without effect.

The remissions of the successfully treated patients lasted from one day to some months. Weekly infusions of  $2\frac{1}{2}$ -10 mgr ACTH, eventually combined with sulphur oil suspension injections, had some effect on the duration of the remission, but not enough to be a practical procedure.

No clear relation was seen between the effect of ACTH on the asthmatic dyspnoe and the effect on the amount of excreted neutral 17-ketosteroids or on the number of eosinophilic cells in the blood. We got the impression that the paroxysmal type of asthma was more susceptible to ACTH than more chronic forms.

In table 20 p.58 the results are given of determinations of the pressure in the pulmonary artery at rest and during effort in 14 patients before and 7 also during treatment with ACTH.

Repeated measurements of the vital capacity were performed before therapy, during placebo treatment, and during the administration of ACTH. During the same periods the vital capacity was determined after administration of histamine intravenously and adrenalin subcutaneously. Examples of the results are given in fig.10-15, p.59-62. A decrease of the sensitivity for histamine was seen in some patients during administration of ACTH.

In table 23 p.63 the results of determinations of the residual volume before, during and sometimes after ACTH therapy are given.

Case reports and figures with individual values on seven representative patients and a table on all treated patients are given in pp. 64-77, fig. 16-23.



In chapter III the relations between bronchial asthma in general and the endocrine system are further explored by a review of the literature, a search for clinical signs of endocrine disorders in 300 asthmatic patients, and by hormone determinations in the urine of asthmatic patients.

A review of the literature on the relations of asthma and endocrines reveals that a hypo- and a hyper-function of almost every endocrine gland has been regarded as the *cause* of bronchial asthma. Hormone determinations in asthmatic persons have been reported by Waldbott and Bailey (estrogenic substances in blood diminished in premenstrual phase in asthmatic women, 1942), Kousmine (gonadotrophic substances, excretion very high in allergic patients of various ages, 7 asthmatics, 1947), Ericksson-Lihr et al. (excretion of neutral 17-ketosteroids about normal in 24 allergic patients, 19 asthmatics, mostly children, 1949), Hioco and Samter (neutral 17-ketosteroids and „glycosteroids“ in urine of 18 resp. 22 asthmatics, normal as compared with 8 controls, 1950), Harvier et al. (neutral 17-ketosteroids in 9 asthmatic patients, excretion diminished, 1950) and Venning et al. (neutral 17-ketosteroids and „glycosteroids“ in urine of 12 asthmatics, both diminished as compared with 30 normal individuals, 1951).

Endocrine disorders were not of any significance in our series of 300 patients (table 25, p.86). Especially hyperthyreoidism was not found, infantilism in 3 or 4 cases. Abnormal menstruation was found in 9 women. The significance of appearance or reappearance of asthma about the age of 50 (resp. in 52 and 23 cases!) in its relation to endocrine function is not clear (table 26, p.87). The same holds true for improvement of asthma during gestation and the unfavourable influence of the premenstrual phase on asthmatic complaints (table 28).

The amount of estrogenic substances was determined in the urine of 10 asthmatic women and 8 asthmatic men; the result, which shows no abnormalities, is given in table 29 p.91. The determinations of these and other hormones were performed by Dr E.Dingemanse† and Dr L.G.Huis in 't Veld. Gonadotrophic substances are determined in the urine of 33 patients, 19 women and 14 men. No abnormal quantities were found (table 30, p.93).

The amount of excreted neutral 17-ketosteroids was determined in the urine of 80 asthmatic patients. The over all results are shown in fig.27, p.94, and fig.28, p. 95. Compared with normal values from the same laboratory and with the same method (Dingemanse, Huis in 't Veld et al.) it is evident that the amount, excreted in the urine, is diminished in male asthmatic patients of all age groups and in the young female patients. In the age group of 40-50 year of the women there was no statistically significant difference between normals and asthmatics. Above the age of 50 in our material the amount of neutral 17-ketosteroids, excreted in the urine, was higher in asthmatic women than in normal women of that age group.

During the course of this study we became convinced, that in asthmatic patients with a purulent, bacterial bronchial infection the amount of neutral 17-ketosteroids in the urine was larger than in non infected asthmatics. The quantity of neutral 17-ketosteroids excreted in 24 hrs by non infected and infected male patients and



non infected and infected female patients is given in table 34-37, p.100-102, and is illustrated in fig. 29 p.102. The excretion in asthmatic patients with a purulent bacterial bronchitis is statistically significant higher than in non infected asthmatic patients. Perhaps the disagreement in the literature concerning the presence of abnormalities in the excretion of 17-ketosteroids in asthmatic patients is partially caused by an unconscious selection of the patients on the point of (bronchial) infections by the various authors.

The increase of the amount of neutral 17-ketosteroids in the urine during a bronchial infection is seen by the author as an expression of a by-action of the purulent bronchitis as a „stressor agent” (Selye): stimulation of the pituitary-adrenal system. In fig. 9 p. 29 it has been shown that during a bronchial infection the number of circulating eosinophilic cells is significantly lower than in a phase without infection.

The influence of a bronchial infection is comparable with that of ACTH not only in its action of the number of eosinophils and the amount of 17-ketosteroids, but also in its action on the asthmatic complaints. In table 38 page 104 the results are shown of a study of 14 infected asthmatic patients, who got a 5 day „successful” antibiotic treatment. 13 of these patients got a lower excretion of 17-ketosteroids, 7 of them became more dyspnoic after antibiotic treatment. Of course one should not overestimate this salutary action of a bacterial bronchitis, because an infection has a local noxious effect.

In the next paragraph the results are given of further differentiation of the neutral 17-ketosteroids in the urines of 22 asthmatic patients. The differentiation of the neutral 17-ketosteroids, elaborated by Dingemanse and Huis in 't Veld<sup>3)</sup>, has been performed by these investigators in their laboratory. The results, compared with values of normal individuals, are shown in fig. 31 and 32, pages 107 and 108. It is obvious that  $\beta$ -17-ketosteroids (i-androstanolen, dehydroepiandrosteron, epiandrosteron), as well as androsteron, etiocholanolon and 11-oxyetiocholanolon and 11-hydroxyandrosteron are diminished in the urine of asthmatic patients. Thus the metabolites of the gonads are as well excreted in small quantities as are metabolites of the adrenal cortex. It has to be stressed that in urines with an extremely low content of ketosteroids no differentiation has been performed, because in these urines a diminution of all fractions may be expected. It can be concluded, that if the lowering of the excretion of 17-ketosteroids should be seen as an expression of a diminished function of the adrenal cortex, a hypofunction of the gonadal glands should also be considered. However, the real significance of the diminution of the amount of 17-ketosteroids in the urine of asthmatic patients, especially of non infected ones, is not known. Theoretically it may be the expression of 1) a hypofunction of the adrenal

3) Dingemanse, E., Huis in 't Veld, L.G., de Laat, B.M., Clinical method for the chromatographic-colorimetric determination of urinary 17-ketosteroids.  
I. J. Clin. Endocrin. 6, 535, 1946.  
II. (with S.L. Hartogh-Katz) J. Clin. Endocrin. a. Metabolism 12, 66, 1952.



cortex and the gonads. 2) an altered metabolism of steroids. 3) a higher consumption in the tissues. 4) an altered excretory function of the kidney. As yet it is not possible to make a choice, although the first possibility seems to be the most probable one. But only few is known about the excretion of 17-ketosteroids in other diseases; therefore the specificity of the low excretion in bronchial asthma may be doubtful.

Adrenal function tests, as insulin tolerance tests, „Thorn tests” with ACTH and adrenalin have been performed in our material and illustrated in fig.33-37, p.112-116. Blood sugar values in asthmatic patients after intravenously administered insulin did not significantly differ from those of the controls (fig.34). The results of Ericksson-Lihr (fig.33), who found an early and severe hypoglycaemic reaction in allergic patients could not be confirmed. The decrease of the number of eosinophilic cells after the administration of ACTH was normal in asthmatic patients. After administration of 0,3 mgr adrenalin subcutaneously the *percentile* decrease of the number of eosinophilic cells in asthmatics was less than the percentile decrease in controls, but in *absolute values* the decrease was greater than in normal individuals. The adrenal function tests as performed in this study do not permit the conclusion that the function of the pituitary-adrenal system in asthmatic patients is disturbed.

In chapter IV our experiments are reported on the diurnal rhythm of the activity of the pituitary-adrenal system (as expressed by the number of circulating eosinophilic cells and the amount of neutral 17-ketosteroids in the urine) and of the ventilatory functions of 12 normal and asthmatic men. The results are summarised in fig.38, p.121. A decrease in ventilatory functions (vital capacity and expiratory velocity) during the night was measured in each of the twelve asthmatic men, often without clinical signs of dyspnoe. In 12 normal men the decrease was much less evident; in the vital capacity of normals no significant difference between day and night values could be demonstrated.

In normals as well as in asthmatics a decrease in the excretion of 17-ketosteroids and an increase of the number of circulating eosinophilic cells during the night could be demonstrated. In the asthmatic patients the excretion of 17-ketosteroids was during the night significantly lower and the number of eosinophilic cells higher than in the normal individuals. Under these circumstances no rhythm in diuresis could be proved in normals or in asthmatics.

The decrease in the respiratory functions during the night in asthmatic patients is a clinically well known fact: 156 of 220 patients were dyspnoic during the night, 107 had more complaints during the night than during the day (table 41, p.120). It is suggested that the nocturnal attack of asthma might be brought about by a decrease of the activity of the pituitary-adrenal system during the evening and night.

By an injection of ACTH at 20.- p.m. the dip in the ventilatory functions could be flattened; the values were significantly higher at 24.-hrs and at 4.- a.m. A nocturnal eosinophilia did not occur and the amount of 17-ketosteroids excreted was a little higher.

In chapter V we gave a summary and conclusions.